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CASE REPORT

Diffuse sclerosing variant of thyroid papillary carcinoma: Diagnostic challenges occur with Hashimoto's thyroiditis

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Diffuse sclerosing papillary thyroid carcinoma (DSPTC) is a relatively rare variant of papillary thyroid carcinoma with distinct histological features, radiological characteristics, and biological aggressiveness. Compared with conventional papillary thyroid carcinoma, DSPTC is characterized by scattered microscopic tumor islands, diffuse fibrosis, calcification, and abundant lymphocytic aggregation. A preoperative diagnosis is challenging in the absence of nodules and scanty fine needle aspiration cytology samples. We describe a unique DSPTC patient, an 18-year-old woman who presented with a neck mass that grew slowly for 2 years. The palpable neck mass was nontender, well defined, firm, and unmovable. Laboratory studies showed normal thyroid function and positive autoimmune markers: antithyroglobulin antibody = 1:1600 and antimicrosomal antibody = 1:1600. A neck ultrasound showed diffusely prominent microcalcifications with one small vague nodule. Hashimoto's thyroiditis with an accompanying malignancy was suspected. Based on the result of intraoperative pathology reports, the patient was given a total thyroidectomy. Lymph node dissection and histological analysis revealed bilateral DSPTC in addition to lymphocytic thyroiditis in nonmalignant areas of the thyroid. Clinical and histological diagnostic challenges usually occur when DSPTC presents with a diffuse thyroid enlargement, dispersed microscopic tumor islands (frequently without mass formation), extensive fibrosis, and abundant lymphocytic infiltration mimicking thyroiditis.

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Introduction

Papillary carcinoma is the most common malignant neoplasm of the thyroid gland. Histological variants of papillary thyroid carcinoma (PTC) are well known and are usually classified as "biologically aggressive" or "biologically indolent."[1,2] Diffuse sclerosing papillary thyroid carcinoma (DSPTC) is a rare variant of PTC with distinct characteristics and is recognized as biologically aggressive. DSPTC occurs at a younger age and has a higher incidence of cervical lymph node metastasis than conventional PTC.[3] Ultrasound findings of DSPTC also reveal diagnostic features: diffuse scattered microcalcifications with or without associated mass in most cases.[4] Fine needle aspiration cytology of DSPTC always reveals numerous psammoma bodies (microcalcifications) in cellular fragments and dispersed microscopic tumor islands of sheets or follicular structures in a lymphocyte-rich background,[5,6] while Hashimoto's thyroiditis shows abundant lymphocytic infiltration and prominent Hurthle cell changes in follicular cells. Because DSPTC always permeates the entire gland, which causes diffuse thyroid enlargement without a dominant nodule, and because histological analysis shows copious inflammation and scattered microscopic tumor islands, the preoperative diagnosis of DSPTC is challenging, whether or not combined with Hashimoto's thyroiditis.

We present a unique case of DSPTC with characteristic ultrasound findings, cytological and histological correlation, and biological behavior, and discuss its clinical evaluation and diagnosis.

Case report

In July 2006, an 18-year-old woman presented at National Cheng-Kung University Hospital with a neck mass that had grown slowly for 2 years. The size of the mass had not changed, but the texture had become firm. The patient did not have any unusual heart palpitations or body tremors, nor had she experienced any change in body weight or poor appetite. She stated that she had difficulty swallowing when she was lying down, that she had recently noticed that she was losing more hair, and that the neck mass was sometimes tender. The patient had no family history of thyroid disease, nor a personal history related to a preexisting thyroid pathologic process or previous irradiation to the neck region.

A physical examination revealed a diffuse palpable middle-neck mass protruding on both sides. The mass was nontender, well-defined, firm, and immovable. An initial ultrasound showed generally enlarged thyroid lobes with diffusely prominent microcalcifications and one vague nodular lesion in the right thyroid lobe (Fig. 1A and B). It also showed enlarged bilateral neck lymph nodes and diffuse microcalcifications similar to those in the bilateral thyroid lobes (Fig. 1C). Thus, fine needle aspiration cytology was performed, which showed atypical cells in flat sheets and clusters with nuclear enlargement, vesicular nuclei, irregular nuclear borders, and abundant cytoplasm (Fig. 2A). Although longitudinal nuclear grooves and intranuclear cytoplasmic inclusions were not shown, a malignancy was highly suspected. A serological analysis showed normocytic anemia (Hb: 9.9 g/dL) and normal thyroid marker values—free T4: 1.24 ng/dL (normal: 0.9–2.0 ng/dL), T3: 72.22 ng/dL (normal: 85–202 ng/dL), T4: 8.13 g/dL (normal: 5.1–14.1 ng/dL), and thyroid-stimulating hormone (TSH): 0.668 mIU/L (normal: 0.27–4.2 mIU/L)—with positive antithyroglobulin antibody (1:1600) and antimicrosomal antibody (1:1600). Hence, Hashimoto's thyroiditis with a suspected accompanying malignancy was the initial diagnosis. A total thyroidectomy and bilateral neck lymph node dissection were performed, and an intraoperative pathology consultation proved its malignancy (lymph node metastasis). The total thyroid glands and bilateral neck lymph nodes were submitted for a pathological examination. Microscopically, all lobes of the thyroid and bilateral lymph nodes contained tumor cells and showed diffuse stromal fibrosis, prominent lymphocytic infiltration, and numerous psammoma-type calcifications.

Postoperative thyroid function tests consistently indicated hypothyroidism; therefore, the patient was given supplements of oral thyroxine (100 μg/d), which she still continues to take. Interestingly, postoperative levels of antithyroglobulin antibody and antimicrosomal antibody gradually diminished and have been undetectable since 5 months after surgery. Moreover, the patient underwent one postoperative radioiodine ablation therapy for lymph node metastasis. Although the tumor initially metastasized to the cervical lymph nodes, at a 3-year follow-up, the patient's chest X-ray was normal and we found no evidence of distal metastasis.

Pathology findings

All tissue samples obtained during surgery were fixed in 10% buffered formalin and processed for histopathologic examination using standard methods. Tissue sections (4 μm thick) were stained with hematoxylin and eosin (H&E). The specimens consisted of tissue from the bilateral thyroid lobes, pyramidal lobe, and bilateral neck lymph nodes. The right lobe, pyramidal lobe, and left lobe measured $7 \times 4 \times 3$, $1.2 \times 0.7 \times 0.5$, and $6 \times 3 \times 3$ cm^3, respectively. When cut, they were firm with diffuse calcifications. In the serial sections, there was one vague, small (about 0.8×0.7 cm^2) nodule in the right lobe (Fig. 1D). The remainder of the right lobe and the other lobes of thyroid were diffusely fibrotic, tan-to-white in color, and without any nodular masses.

Histological analysis showed diffuse squamoid tumor nests of DSPTC in all three lobes of the thyroid, diffuse and prominent stromal fibrosis, prominent lymphocytic infiltration with lymphoid follicle formation, and numerous psammoma bodies (Fig. 2B and C). There were many tumor emboli of small papillary structures in the lymphatic channels (Fig. 2D). A cytological analysis of the DSPTC tumor cells revealed large nucleoli, pale nuclei, and abundant cytoplasm in squamoid nests and follicular structures (Fig. 3A), different from the classical cytology of PTC. Only the small, vague, nodular lesion of the right thyroid lobe appears similar to a conventional papillary carcinoma (Fig. 3B and C), which has nuclear grooves, intranuclear inclusions, and ground glass nuclei in its papillary and follicular structures. The non-neoplastic follicles were also infiltrated by dense lymphocytic

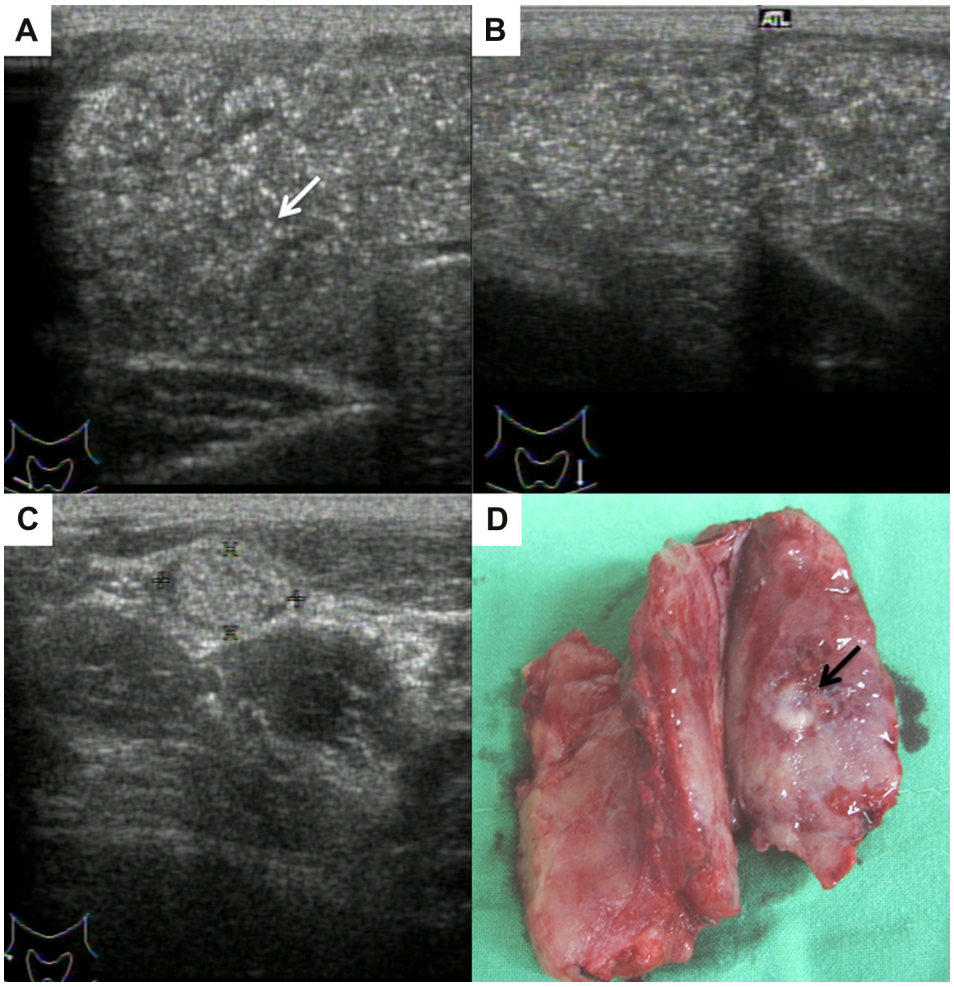

Figure 1 Bilateral (A: right-transverse view; B: left-longitudinal view) enlarged thyroid lobes with diffusely bilateral prominent microcalcifications and one vague mass of right thyroid (white arrow). Bilateral enlarged lymph nodes (C: right-transverse view) also reveal diffuse microcalcifications. The right perithyroid lymph node is 1.11 × 0.67 cm^2. (D) The only vague small nodule (black arrow; about 0.8 × 0.7 cm^2) in the right lobe in the thyroid. Except for the nodular lesion, the thyroid was firm and fibrotic.

follicles. However, there were no prominent oncocytic changes in these areas. The lymph nodes (pretracheal: 6/7; right neck: 8/10; and left neck: 8/11) contained extensively metastatic carcinoma characterized by squamoid nests of tumor cells in a sclerosing background and numerous psammoma bodies (microcalcifications) (Fig. 3D), which correspond to the ultrasound findings for lymph nodes.

Discussion

We reported the case of a patient presenting with normal thyroid function, positive antithyroglobulin antibody and antimicrosomal antibody, and diffuse thyroid enlargement, resembling Hashimoto's thyroiditis but postoperatively confirmed as DSPTC. Although DSPTC is rare, it is important for physicians to recognize and consider the possibility of this disease because of its clinical resemblance to Hashimoto's thyroiditis.[7,8] In one series of 14 patients,[7] four cases were misdiagnosed and treated as Hashimoto's thyroiditis for a mean period of 3.8 years. In the absence of a nodular mass or an atypical cell in fine needle aspiration cytology samples, the clinical presentation may result in a misdiagnosis.

In our patient's thyroid function tests prior to operation, relatively low T3 level was noted with normal T4 and TSH. Hence, we further checked her free T4 level, which was normal again. Since then, low T3 syndrome describing a situation characterized by lowered T3 levels with normal thyroid gland activity was also taken into differential diagnosis. Low T3 syndrome is the most common form of euthyroid sick syndrome which is divided into three types—low T3 syndrome, low T3 and T4 syndrome, and low TSH syndrome.[9] Euthyroid sick syndrome represents abnormalities of thyroid hormone concentrations associated with a wide variety of nonthyroidal illnesses. Except thyroid malignancy, our patient had no specific underlying disease or medication. Furthermore, the low T3 level prior to operation may be appropriately taken as an additional finding probably associated with underlying malignancy.

In a series of 30 cases,[10] DSPTC occurred at a significantly younger age (mean age: 30.4 years), showed some lymph node metastasis (in five of 30), recurred more frequently (in nine of 30), was more likely to manifest

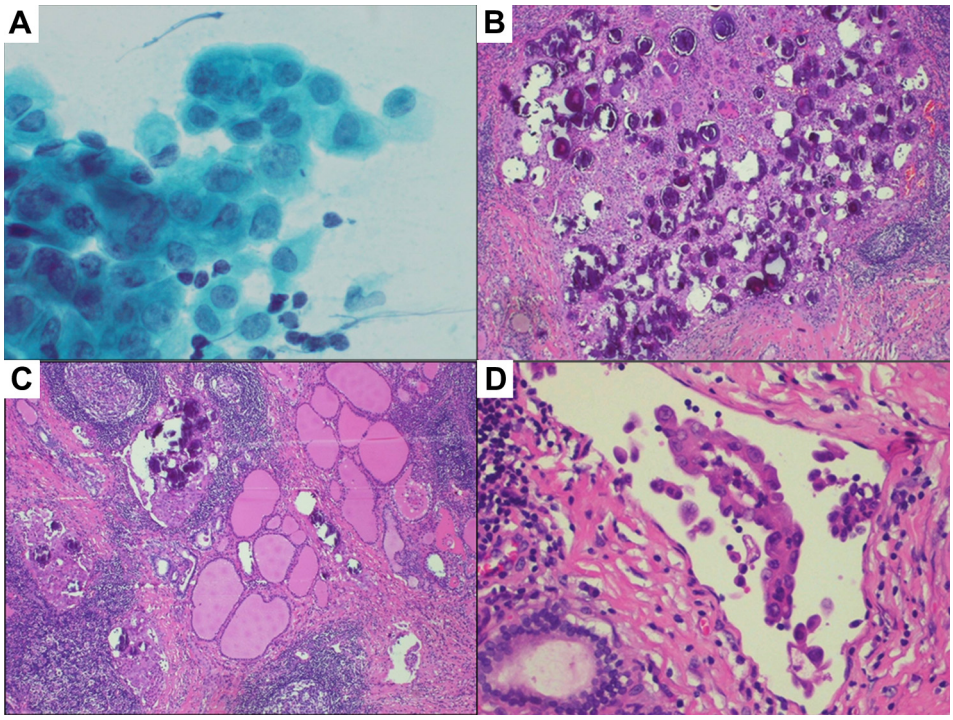

Figure 2 (A) Fine needle aspiration cytology (*Papanicolaou's* stain, 400×) revealed atypical cells in flat sheets and clusters. The atypical cells show overlapping of nuclei, enlarged vesicular nuclei, irregular and distinct nuclear borders, and abundant cytoplasm. Longitudinal nuclear grooves and intranuclear cytoplasmic inclusions are not obviously shown. The background is lymphocyte rich. (B and C) Squamoid tumor nests diffusely distributed in all thyroid lobes with dense stromal fibrosis, prominent lymphocytic infiltration with lymphoid follicle formation, and numerous psammoma bodies (H&E stain, 40×). (D) Tumor emboli of small papillary structures in the lymphatic channels (H&E stain, 200×). H&E = hematoxylin and eosin.

distant metastasis (especially lung), had worse disease-free survival (60.9% in a 10-year follow-up), and expressed a higher incidence of positive antithyroglobulin antibody (72%, 23 of 32) in comparison with all other PTC variants. Our patient presented with most of the typical characteristics. Because it is an aggressive cancer that clinically mimics Hashimoto's thyroiditis, a thorough clinical evaluation is important for avoiding a misdiagnosis and mistreatment.

Ultrasound evaluation may be helpful initially because the diagnostic features of DSPTC include a heterogeneous echotexture, solid composition, ill-defined margins, and diffuse microcalcifications with a snowstorm appearance in thyroid lobes with or without an associated mass in most cases,[4,5] which corresponds to our findings (Fig. 1A and B). The diffuse nature of DSPTC often mimics chronic thyroiditis on ultrasound images and leads to treatment delay, especially in the absence of a nodular mass. The most important ultrasound features may be snowstorm-like microcalcifications in enlarged lymph nodes (Fig. 1C), which is characteristic of DSPTC, even when there are no significant thyroid nodular lesions.

Fine needle aspiration cytology of DSPTC tumors always reveals numerous psammoma bodies, abundant lymphocytes, metaplastic squamoid cells, and the absence of stringy colloids together with few epithelial cells that show the classical features of papillary carcinoma, such as nuclear grooves, intranuclear inclusions, and ground glass nuclei.[5,6] The patient in our case showed clusters of atypical epithelial cells in a lymphocyte-rich background with abundant cytoplasm, enlarged vesicular nuclei, and irregular nuclear shapes. Although the nuclear grooves and intranuclear cytoplasmic inclusions were not obvious, a malignancy was highly suspected. Moreover, sampling failures and misinterpretations of diffuse tumor cells may occur in DSPTC cases because clinicians may take scanty and unrepresentative tissue samples randomly from a diffuse fibrotic, inflamed, and microcalcified thyroid, especially in the absence of significant nodular mass. Hence, the sensitivity rate of fine needle aspiration cytology for those without nodular lesions may not be as high as in the cases reported in the literature.[5,6]

For the general treatment of PTC, a total thyroidectomy or bilateral lobar resection results in fewer recurrences than a lobectomy. DSPTC treatment in our center uses the same protocol as is used for ordinary PTC: a total thyroidectomy and then radioiodine or external radiotherapy in selected cases. The good clinical outcome in our DSPTC case might have been related to the patient's youth, the treatment, or both.

A general concern when following up PTC is that thyroglobulin is a sensitive and specific serum marker for detecting relapses. However, its effectiveness is limited by the presence of antithyroglobulin autoantibody, which may interfere with thyroglobulin assays. The high level of antithyroglobulin autoantibody (72—75%) in DSPTC[7,8,10,11] may render it less useful as a tumor marker after radioiodine ablation. Also, our young patient initially had high

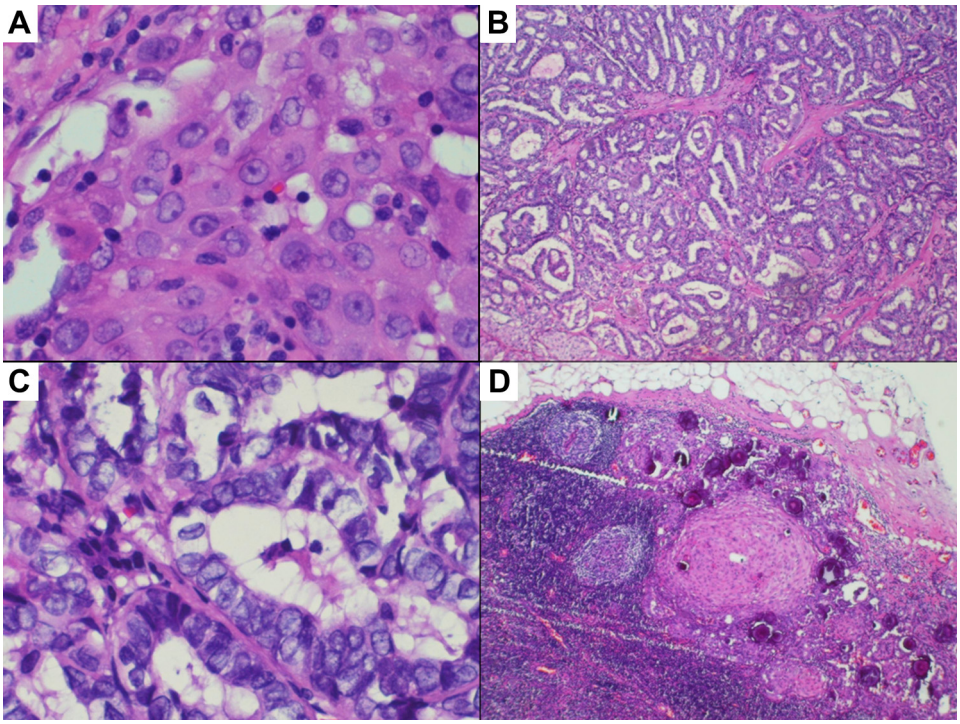

Figure 3 (A) Cytology of DSPTC tumor cells reveals large nucleoli, pale nuclei, and abundant cytoplasm in squamoid nests and follicular structures (H&E stain, 400×). (B) The vague nodular lesion in the right thyroid appears similar to a conventional papillary carcinoma in papillary and follicular structures (H&E stain, 40×). (C) Tumor cells in the vague nodular lesion of the right thyroid show nuclear grooves, intranuclear inclusions, and ground glass nuclei (H&E stain, 400×). (D) Metastatic carcinomas in lymph nodes reveal squamoid nests of tumor cells in a sclerosing background and numerous microcalcifications, which are characteristic of DSPTC (H&E stain, 40×). H&E = hematoxylin and eosin.

levels of antithyroglobulin and antimicrosomal antibodies, but their postoperative levels gradually diminished and have been undetectable since 5 months post-surgery. Apart from this, the follow-up for patients with DSPTC is similar to that for patients with other PTC variants.

In conclusion, because patients with DSPTC may present with typical clinicopathological features and initially appear to have Hashimoto's thyroiditis, a thorough clinical evaluation and an early diagnosis are important. DSPTC generally has a greater tendency for lymph node metastasis and distant metastasis, and worse disease-free survival than other PTC variants. Complete surgical treatment and postoperative radioiodine ablation are recommended, and a close follow-up is necessary.

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